UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/838,486	04/07/97	BAEKKESKOV S	02307U-3122

HM22/0705

TOWNSEND AND TOWNSEND AND CREW
TWO EMBARCADERO CENTER 8TH FLOOR
SAN FRANCISCO CA 94111-3834

EXAMINER	
TUNG, M	
ART UNIT	**PAPER NUMBER**
1644	18

DATE MAILED: 07/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/838,486	Baekkeskov, et al.
Examiner	**Group Art Unit**
Mary B. Tung	1644

☒ Responsive to communication(s) filed on *Apr 14, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *31, 34, 35, 38-42, and 49-61* is/are pending in the applicat

Of the above, claim(s) *38-42* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *31, 34, 35, and 49-61* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *31, 34, 35, 38-42, and 49-61* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-30 and 43-48 were cancelled in the preliminary amendment filed April 7, 1997.

2. Claims 32, 33, 36 and 37 have been cancelled in the amendment filed Nov. 2, 1998 Paper No. 9).

3. Non-elected claims 38-42 were withdrawn from consideration by the Examiner in the paper mailed April 28, 1998 (Paper No. 6).

4. Claims 49-57 were added in the amendment filed Nov. 2, 1998, Paper No. 9.

5. Claims 58 and 59 were added in the amendment filed 7/28/99, Paper No. 13.

Claims 60 and 61 were added in the paper filed 4/14/00, Paper No. 17.

6. Claims 31, 34, 35, 38-42, 49-61 are pending in this application.

Continued Prosecution Application

7. The request filed on for a Continued Prosecution Application (CPA) under 37 C.F.R. 1.53(d) based on parent Application No. 08/838,486 is acceptable and a CPA has been established. An action on the CPA follows.

8. The Examiner acknowledges the discussions with Mr. Liebeschuetz, Biotech Specialist Richard Schwartz, SPE Christina Chan and Examiner Mary Tung on 3/21/00. Several issues were raised, including whether the 64 kD antigen of the cited art and the 65 kD antigen of the instant application are the same. Mr. Liebeschuetz also stated on 3/21/00 that the terms 64kD, 65 kD and 67 kD antigens, GAD and pancreatic autoantigen, "were simply different names for the same thing". Mr. Liebeschuetz stated during the interview and again in the reply in Paper No. 17 has confirmed that the two antigens are the same.

9. The second issue that was raised by Mr. Liebeschuetz concerned what he believed to be similar claims in issued patents 5,762,937, 6,001,360 (both by Atkinson, et al.) and application No. 08/455,725 (identified by Applicants as being by Tobin). It is noted by the Examiner that US Patent No. 6,001,360 (issued Dec. 14, 1999) issued subsequent to the action mailed 10/14/99. As all issued patents are presumed valid, the Examiner will not comment in this or in any other action about the validity or other matters concerning the issued patents, nor on pending applications, as required under 35 U.S.C. 122 and 37 C.F.R. 1.14. Therefore, the Applicants' comments in paragraph 10 will not be addressed.

10. It is acknowledged by the Examiner that the Applicants have disclosed in Paper No. 17, that new claims 60 and 61 were copied from US Patent No. 6,001,360, claims 1 and 2, in accordance with 37 C.F.R. 1.607(c) *(MPEP 2001.06(d))*.

11. The Examiner also notes that a discussion concerning the "937 patent was made in the action mailed 10/14/99 (Paper No. 14) and that the Applicants argued that there is "inconsistency between the maintenance of the rejection in the present application, and the issuance or indication of allowability of substantially similar claims in two other patent filings having priority dates approximately contemporaneous with that of the present application." Applicants' asserted that the instant claims are allowable because similar claims have issued or been allowed in other cases was rendered moot because the prosecution of each case is unique to the facts of each case, and upon the assumption of validity of issued patents. The Examiner also noted to Applicants that the claims of the '937 patent by Atkinson, et al. are not co-extensive in scope.

12. The Applicants also stated in the response in Paper No. 17 that "the Examiner may no longer adhere to all of the views expressed in the office action in light of the above interview". In light of the interview on 3/21/00 and the amendment filed in Paper No. 17, the following rejections remain:

Claim Rejections - 35 U.S.C. § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Applicant's arguments filed in Paper No. 17 have been fully considered but they are not persuasive.

15. Claims 31, 34, 35, 49-59 and newly-added claims 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

16. The goal of peptide immunotherapy of T-cell-mediated autoimmunity is to induce anergy in self reactive T cells. Therefore, the pathologies of autoreactive T cells in autoimmunity can be blocked by using the appropriate autoantigen or autoantigen-derived peptides (see Tisch, et al., *(Proc. Natl. Acad. Sci. USA 91:437-438, 1994)*, page 437, col. 1, in particular). However, the effectiveness of this therapy hinges on

several factor: one is whether the therapy can be used to treat an ongoing autoimmune response or whether it is useful only in preventing the disease. Typically, an autoimmune disease is diagnosed at the time of onset when significant tissue damage has already occurred. The onset of IDDM is not predicable and therefore, prophylaxis of these diseases is not currently possible; currently, therapy is initiated in these conditions only after the onset of disease symptoms. Furthermore, Tisch et al.,*(Proc. Natl. Acad. Sci. USA 91:437-438, 1994)* teach that treating an ongoing T-cell-mediated autoimmunity by administering an antigen peptide may have an immunizing effect and exacerbate the disease condition (*(Proc. Natl. Acad. Sci. USA 91:437-438, 1994)*, page 437, column 3, in particular). How the antigen is administered is also a key factor in determining whether an immunogenic or tolerogenic response is induced. The duration of the toleragenic effect is an additional factor. Frequent treatment over a prolonged period of time may result in unforseen immunological complications. Furthermore, the Applicant discloses on page 20, lines 16-19, that "care should be taken that administration of the pharmaceutical compositions of the present invention does not potentiate the autoimmune response." There is a lack of guidance in the specification as to how the potentiation of the autoimmune response would be prevented using the instant invention. Additionally, the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS, IDDM and rheumatoid arthritis, in which there are responses to several antigens (*(Tisch, et al., Proc. Natl. Acad. Sci. USA 91:437-438, 1994)*, see page 437, col. 2 ¶ 3 and bridging over to col. 3, ¶ 4). Additionally, Lernmark *(J. Int. Med. 240:259-277, 1996)* teaches that "The mechanisms of GAD65-induced protection of spontaneous diabetes is critical to our understanding of autoimmune diabetes. Further experiments also extended to the spontaneously diabetic BB rat are warranted to determine the mechanism of protection, especially as other investigators have not found the published procedures to be easily reproducible." (*(J. Int. Med. 240:259-277, 1996)*, see page 274, col. 2, paragraph 1, in particular). Additionally, Harrison *(Molec. Med. 1:722-727, 1995)* teaches that "Insulin and GAD are strong candidate toleragens for the prevention of human IDDM. However, caution should be exercised with GAD because, unlike insulin, it is not β cell specific and is found in high concentrations in the brain as well as in peripheral tissues other than islets. Without further animal studies and knowledge of the GAD epitopes that elicit T cell reactivity unique to human β cells, it would seem unwise to manipulate immunity to this widely distributed key enzyme. For the present, insulin (or proinsulin) is the only islet antigen that, both on scientific and ethical grounds, justifies therapeutic application to humans at risk of IDDM." (*(J. Int. Med. 240:259-277, 1996)*, see page 724, col. 2, paragraph 2, in particular). Applicant has provided only in vitro experiments demonstrating the identity of GAD in rat islets of Langerhans and in rat brain, and anti-GAD antibodies in the sera of patient with IDDM and stiff man syndrome, to demonstrate operability of the claimed polypeptide. Since human and rats display different major histocompatibility complex haplotypes and Applicant has given no guidance as to how their peptide

specific therapy would overcome autoreactive T cell escape mechanisms in humans or whether the peptide would induce autoimmunity or tolerance, it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

17. The Applicants argue that during the interview (on March 21, 2000), that the Examiner "drew Applicants' attention to a reference hitherto not of record *(Petersen, et al., Autoimmunity, 25:129-138, 1997)*." The Applicants further allege that "Because rats are a somewhat larger rodent than mice, the Examiner apparently views rats as being more predicative of humans than mice." In contrast, the Examiner was merely demonstrating that in a more recent (1997) publication, a different animal model teaches that treatment with GAD65 does not protect against diabetes and Petersen teaches that "neither GAD65 nor BSA autoimmunity is important for the development of diabetes in BB rats, in contrast to the situation in NOD mice, and further emphasizes that extrapolation from only one animal to autoimmune diabetes in general may not be appropriate." (see the abstract). Since the Applicants own disclosed experiments used rat islet cells (see Figure 1 of the specification), the Examiner maintains that it is an appropriate model, absent any evidence provided by the Applicants that the BB rats model is not predicative of human disease. The reference also teaches that "One of the limitations in extrapolating data from an animal model like the NOD mouse, is that it represents only one genotype, whereas IDDM in humans in all probability has a much more multifaceted etiology, pathogenesis and genetic predisposition." (see page 130, col. 1). Applicants admit on page 5 of the response in Paper No. 17, that 20% of IDDM patients presumably have a different genetic predisposition.

18. The argument of Applicants that GAD is a good therapeutic agent because it is the major autoantigen of IDDM is disputed by the teachings of Petersen, et al *(Diabetes, 44:1478-1484, 1994)*, which teaches the use of the 65 kDa GAD in neonatal NOD mice. Petersen also teaches that "Since we have demonstrated that mouse islets contain only very little GAD, the reported T-cell reactivity against mouse islets proteins will most likely have to be explained by other autoantigens. Taken together, these observations show that although GAD autoimmunity is necessary, it is not sufficient for the development of NOD mouse diabetes." (see page 1482, col. 2). Peterson, et al. additionally teach that GAD_{65} could prevent spontaneous diabetes in NOD mice, but that autoantibodies to GAD were detected in injected mice. This seemingly contradictory data is explained by Petersen by saying that the "autoantigenic properties of GAD in NOD mice islets are not well understood." (see page 1482, col. 2, last paragraph).

Claim Rejections - 35 U.S.C. § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the Applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the Applicant for patent.

20. Claim 31 stands rejected under 35 U.S.C. 102(e) as being anticipated by Atkinson (US Patent No. 5,762,937).

21. The '937 patent teaches a method for inhibiting the development of IDDM comprising the administration of GAD to a patient is taught in col. 4, lines 40-48 and col. 25 line 53 and bridging over to col. 26, line 14. The administration of a therapeutically-effective dosage is inherent in the successful treatment of any disease. Therefore, the reference teachings anticipate the claimed invention. Any arguments regarding enablement are moot, since the claimed invention of an issued US patent is to be presumed valid.

22. A method for inhibiting the development of IDDM comprising the administration to a patient GAD is taught in col. 4, lines 40-48 and col. 25 line 53 and bridging over to col. 26, line 14. The administration of a therapeutically-effective dosage is inherent in the successful treatment of any disease. Therefore, the reference teachings anticipate the claimed invention. The rejection as cited in Paper No. 11 was inadvertently cited as 102(a). The Examiner thanks the Applicants for correction of this typographical error.

23. It is noted that the Applicants have not provided any arguments regarding the outstanding rejection under 35 U.S.C. 102, and that the rejection over the '937 patent can be resolved by interference.

Claim Rejections - 35 U.S.C. § 103

24. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

25. It is acknowledged that the Applicants have stated in Paper No. 13 that the subject matter of all claims was commonly owned by the University of California and Yale University.

26. Claims 35 and 54-57 stand rejected under 35 U.S.C. 103(a) as being obvious over Chang and Gottlieb *(J. Neurosci. 8(8):2123-2130, 1988)*.

27. Chang and Gottlieb *(J. Neurosci. 8(8):2123-2130, 1988)* teach the use of GAD in a pharmaceutical preparation by immunizing a mouse with purified rat brain GAD in a composition comprising GAD and Freund's adjuvant (see page 2124, col. 2, paragraph 3, in particular). Chang and Gottlieb do not teach a composition comprising GAD in a pharmaceutically-acceptable carrier for use in humans. However, one of ordinary skill in the art at the time the invention was made would have been motivated to provide a pharmaceutically-acceptable carrier for humans in light of the teaching by Chang and Gottlieb of a pharmaceutically-acceptable carrier for use in rats. Additionally, pharmaceutical carriers are well known to one of ordinary skill in the art for use in humans. Claims 54-56 are included because a product is a product, regardless of its source. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

28. The Applicants argue that laboratory buffers are not manufactured under GMP conditions and thus are not suitable for use in humans. This argument is found unpersuasive, because the conditions under which the buffers are manufactured are not recited in the claims, nor do such conditions render the composition patentable distinct from the prior art teaching. Thus the rejection stands.

The following are new grounds of rejection:

29. Claims 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no support in the specification or claims as originally filed for a method for preventing or delaying the development of clinical symptoms of insulin dependent diabetes, as recited in claim 60. The claim differs in scope with the disclosure in the instant case. Applicants are invited to provide the Examiner with the location in the specification where the above wording is supported. **This is a new matter rejection.**

Conclusion

30. Papers related to this application may be submitted to Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). THE CM1 FAX CENTER TELEPHONE NUMBER IS (703) 305-3014 or (703) 308-4242.

31. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mary Tung whose telephone number is (703)308-9344. The Examiner can normally be reached Tuesday through Friday from 8:30 am to 5:30 pm, and on alternating Mondays. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1640 receptionist whose telephone number is (703) 308-0196.

June 30, 2000
Mary B. Tung, Ph.D.
Patent Examiner
Group 1640

John J. Doll, Director
Technology Center 1600